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ORIGINAL ARTICLE

Primary sclerosing cholangitis: outcome of patients undergoing restorative proctocolecetomy for ulcerative colitis

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Abstract
Purpose The prevalence of primary sclerosing cholangitis (PSC) among patients with ulcerative colitis needing proctocolectomy is about 12%. The study aim was to evaluate the progression of the liver disease after surgery.
Methods PSC progression in 68 patients with UC after restorative proctocolectomy was evaluated after a median follow-up of 11 years (range 0 to 21). Magnetic resonance imaging (MRI) of the liver, histological examination of a core needle liver specimen, and liver function tests were used in addition to clinical history.
Results Of the 68 patients, 30 participated in follow-up examinations. Ductal changes in MRI suggesting a diagnosis of PSC occurred in 21 (72%) of them. One carcinoma of the gallbladder was found in MRI. Histopathologic changes suggesting PSC were observable in 15 (50%) patients. Compared to stage in peroperative biopsies taken at proctocolectomy, PSC stage increased in four (13%) patients, decreased in 15 (50%), and remained unchanged in 11 (37%). Immunohistochemical staining for cytoceratin-7 in hepatocytes was positive in nine (30%) indicating cholestasis. After IPAA surgery, five patients underwent liver transplantation at 1, 1, 5, 6, and 11 years, respectively. Of the 68, six patients have, to date, developed cholangiocarcinoma.
Conclusions Progression of PSC in patients with minor ductal changes at the time of restorative proctocolectomy is unlikely. Those patients with more advanced disease at surgery are at risk for disease progression and liver transplantation. We lack accurate diagnostic methods to detect premalignant changes of the biliary epithelium.

Keywords Primary sclerosing cholangitis · Ulcerative colitis · Restorative proctocolectomy · Cholangiocarcinoma

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Introduction

Primary sclerosing cholangitis (PSC) is closely linked to ulcerative colitis (UC). PSC affects some 3% to 8% of UC patients and conversely, incidence of UC among patients with PSC ranges from 60% to 72% [1–4]. Incidence of PSC among patients with UC requiring surgery reaches about 12% and is thus higher than among patients with UC overall [5].

The natural development of PSC among UC patients after proctocolectomy is unknown, and prediction of PSC progression has been generally difficult [6]. Only serum bilirubin, histological stage in liver biopsy, age, and presence of splenomegaly have served as independent predictors of survival in advanced disease [7]. Early recognition of premalignant biliary epithelium and prevention of cholangiocarcinoma have been impossible, because diagnostic methods are insufficiently sensitive and specific. In patients with severe biliary strictures and cirrhosis or precirrhosis, trypsinogen-2 has been the most accurate and promising means for differentiating PSC from PSC with simultaneous cholangiocarcinoma [8]; hCG-beta, TATI,

trypsinogen-1, CA 19-9, and CEA are also of some value. Trypsinogen-2-alfa1-antitrypsin (T2AAT) fails to differentiate between PSC and PSC with cholangiocarcinoma [8], although it may prove useful in differentiating biliary tract cancer from benign disease [9]. Until now, no medical treatment has proven beneficial for PSC. Ursodeoxycholic acid has not improved survival nor had any beneficial effect in prevention of cholangiocarcinoma [10].

Earlier, we found an unexpectedly high incidence of non-symptomatic PSC in patients with UC needing restorative proctocolectomy [5]. Here, we evaluate progression of PSC in these patients and their need for regular follow-up.

Materials and methods

In the 19-year period from April 1985 to February 2004, of 631 patients with UC, 68 had findings suggesting diagnosis of PSC at the time of restorative proctocolectomy. Indication for proctocolectomy was steroid-dependent disease in 31 patients, dysplasia in colorectal biopsy in 23 patients, cancer in five patients, and fulminant colitis in nine patients. In the first part of that period, suspicion was mainly based on liver function tests [11], but later, all patients having surgery for UC underwent a peroperative core needle liver biopsy [5]. Since then, nine of these 68 have died, five for other than PSC-related causes. Three patients underwent liver transplantation before restorative proctocolectomy and five patients after it; two patients moved abroad. The remaining 49 patients were invited to participate in a follow-up study to investigate any possible progression of their liver disease postoperatively (Fig. 1). Two patients were unavailable; sixteen refused participation in MRI and liver biopsy. Of the 47 patients, 30 (64%), 17 women and 13 men, participated in the study and gave their informed consent. Of these 30, eight (27%) patients already had a diagnosis of PSC before restorative proctocolectomy, whereas 22 had the diagnosis on the basis of liver biopsy at

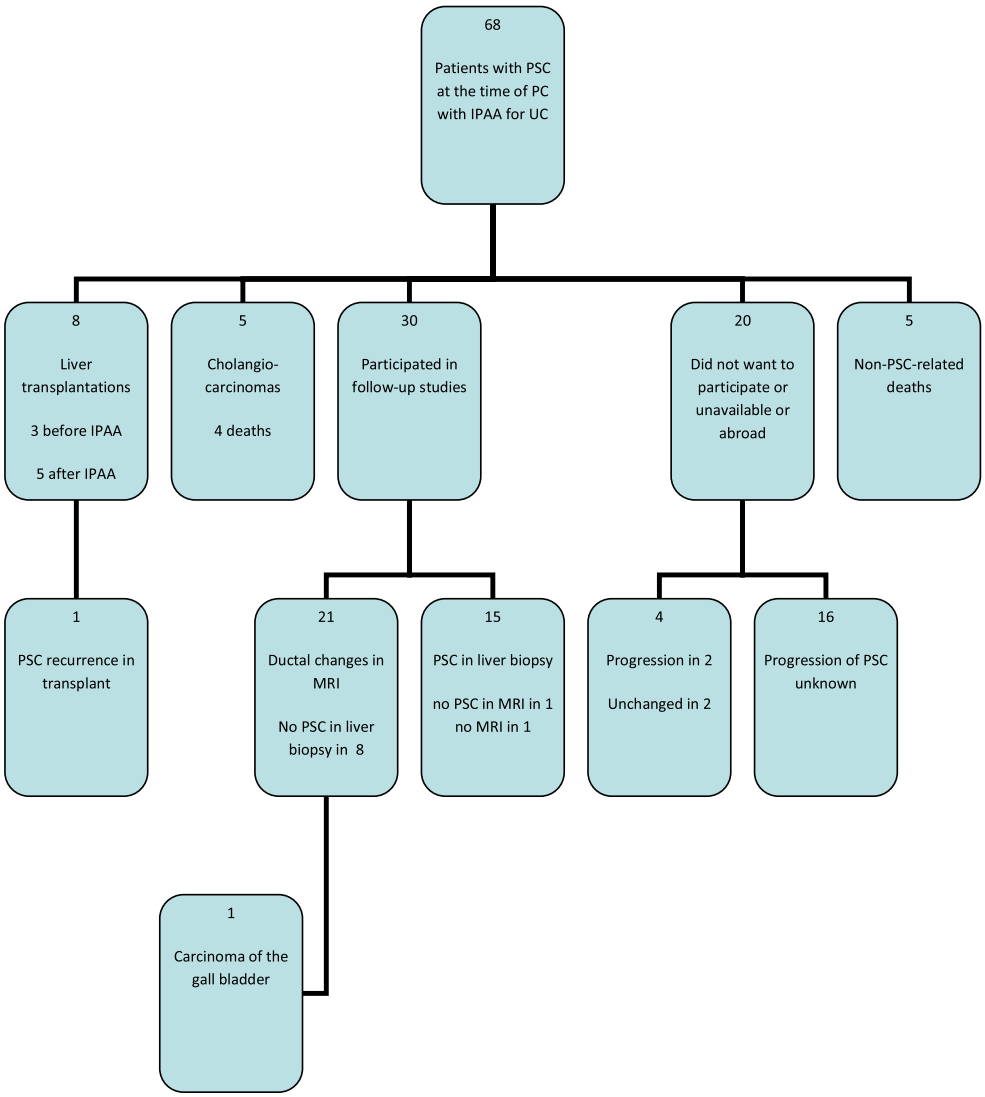

Fig. 1 Outcome of primary sclerosing cholangitis (*PSC*) in patients with ulcerative colitis (*UC*)-related PSC at the time of restorative proctocolectomy (*IPAA*). *MRI* magnetic resonance imaging

Table 1 Ductal scoring system in magnetic resonance imaging (MRI)

Intrahepatic ducts	
0	No visible abnormalities
1A	1 to 3 strictures; normal caliber of bile ducts or minimal dilatation
1B	Multiple strictures (>3); normal caliber of bile ducts or minimal dilatation
2A	1 to 3 strictures; saccular dilatations, decreased arborization
2B	Multible strictures (>3); saccular dilatations, decreased arborization
3	Only central braches seen; diffuse severe pruning
Extrahepatic ducts	
0	No visible abnormalities
1	Slight irregularity of duct contour; no stricture
2A	One segmental stricture
2B	Multiple segmental strictures
3	Stricture almost entire length of duct
4A	Extremely irregular margin; diverticulum-like outpouchings
4B	Extremely irregular margin and strictures ; diverticulum-like outpouchings

the operation. Of these 30, nine patients were on ursodeoxycholic acid therapy and 21 were not. Of all 68 patients, patient histories were retrospectively studied. Follow-up time was a median 11 years (range 0 to 21). The study was approved by the local ethics committee.

Patients underwent magnetic resonance imaging (MRI) of the upper abdomen (Philips Achieva 3.0T, Quasar Dual, Philips Medical Systems, Oriola) and ultrasound-guided core needle liver biopsy. Liver function tests (alkaline phosphatase, bilirubin) were run on serum samples. One radiologist (S.K.) performed the core needle biopsies, and two radiologists (S.K. and L.K.) in consensus interpreted MRIs according to a ductal scoring system (Table 1). One pathologist (J.A), specialized in liver pathology, made the histopathological examination of the core needle biopsies. Ludwig's staging of PSC was based on extent of inflammation and fibrosis on liver biopsy [12]. In addition, the presence of cytokeratin-7 in hepatocytes was investigated by immunohistochemical staining as an additional marker for chronic cholestasis [13, 14].

Correlations between MRI and histological findings and between use of ursodeoxycholic acid and PSC progression were calculated by the Spearman rank correlation test, and $p<0.05$ was considered significant.

Results

Outcome of PSC after IPAA

Of 68 patients with UC-related PSC at the time of restorative proctocolectomy (Fig. 1), five (8%) had liver transplantation after IPAA because of PSC and six (9%) developed cholangiocarcinoma; five of the latter died. Based on follow-up examinations, of 29 patients 21 (72%) had ductal changes in MRI, and of 30, 15 (50%) had diagnostic features of PSC in their core needle liver specimens. On the basis of the patient histories, of 20 patients not participating in follow-up studies, four were in clinical follow-up because of PSC, and 16 were not; in two of the four, slight progression of ductal changes occurred in ERCP and MRI, but the other two had no progression.

MRI

One patient refused MRI because of claustrophobia. In the remaining 29 patients, quality of MRI was considered good in 11 (38%), moderate in 16 (55%), and poor in two (7%). Ductal changes suggesting the diagnosis of PSC occurred in 21 (72%) patients; a total of 21 (72%) patients had changes in their intrahepatic bile ducts and eight (28%) in the extrahepatic bile ducts (Table 2). All these eight patients also had intrahepatic changes. Intensification of the bile ducts was observable in none.

Table 2 Ductal score of 29 primary sclerosing cholangitis patients in magnetic resonance imaging

Intrahepatic ducts	
0	8 (28%)
1a	3 (10%)
1b	10 (3%)
2a	3 (10%)
2b	5 (17%)
Extrahepatic ducts	
0	21 (72%)
1	2 (7%)
2a	1 (3%)
2b	1 (3%)
3	4 (14%)

Seven (24%) patients had non-PSC-related hepatic parenchymal changes in MRI: one (3%) had suspicion of hepatic cirrhosis, one had two hemangiomas, and four (14%) had hepatic cysts. Gallbladder stones were visible in two (7%), and four (14%) previously had undergone cholecystectomy. Pathologic intensification of the gallbladder wall evoked a suspicion of malignancy in one; he underwent cholecystectomy and hepatic resection. The diagnosis was adenocarcinoma of the gallbladder in the final specimen, and one metastatic lymph node appeared beside the neck of the gallbladder. In addition, 13 (45%) patients had findings in other organs: one patient had tumor in his right kidney and underwent nephrectomy, eight patients had renal cysts, three had slight splenomegaly, and one patient had splenic hemangioma. All three with splenomegaly had both intra- and extrahepatic bile duct changes.

Histopathologic examination of liver biopsy

The quality of core needle biopsy in all patients was considered good. Histopathologic changes suspicious for PSC occurred in 15 (50%) patients, eight (27%) had stage I changes, four (13%) stage II changes, and three (10%) stage III (Table 3). Histopathologic stage of the disease correlated positively with ductal score in MRI (correlation coefficient 0.450; $p<0.05$). One of these 15 patients had no ductal changes in MRI, and the one not undergoing MRI because of claustrophobia had stage III PSC in histopathologic examination. Compared to peroperative specimens taken at proctocolectomy: stage of PSC increased in four (13%) patients, decreased in 15 (50%), and was unchanged in 11 (37%). For two patients without changes in the core needle biopsy, but with a stage II disease in the peroperative biopsy and both intra- and extrahepatic changes in MRI, sampling error was implicated. Immunohistochemical staining for cytoceratin-7 was positive in nine (30%) and correlated positively with morphological stage of disease (correlation coefficient 0.646; $p<0.01$) and with ductal score in MRI (correlation coefficient 0.401; $p<0.05$).

Table 3 Histopathologic changes in 30 liver biopsies for primary sclerosing cholangitis

Stage of PSC (0–4)	
0	15 (50%)
I	8 (27%)
II	4 (13%)
III	3 (10%)
Stage of fibrosis (0–4)	
0	20 (67%)
1	7 (23%)
2	3 (10%)
Stage of portal inflammation (0–3)	
0	18 (62%)
1	10 (33%)
2	2 (7%)
Stage of interphase inflammation (0–3)	
0	26 (87%)
1	4 (13%)
Stage of lobular inflammation (0–2)	
0	28 (93%)
1	2 (7%)
Stage of inflammation activity (0–3)	
0	25 (83%)
1	5 (17%)

Liver function tests

The concentration of serum alkaline phosphatase was elevated in nine (7%) patients and of serum bilirubin in three (2%) patients. Neither correlated in MRI with the morphological stage nor ductal score.

Liver transplantation

Three patients underwent liver transplantation 2, 5, and 6 years before their IPAA surgery and five afterwards at 1, 1, 5, 6, and 11 years, respectively. Two liver transplantations were done because of stage IV PSC before the IPAA surgery, and one patient with PSC underwent pancreaticoduodenectomy because of suspicion of malignant stricture in the common bile duct. This turned out to be benign, but liver transplantation was later necessary for a stricture in the biliary anastomosis before the IPAA surgery. Of the five patients having liver transplantation after IPAA surgery, four had stage III PSC, and one had stage IV PSC in the peroperative liver biopsy; their PSC was already diagnosed before the IPAA. One patient developed PSC also in her liver transplant 4 years later.

Cholangiocarcinoma

Of 68, a total of six (9%) patients have thus far developed cholangiocarcinoma. Two of these six were diagnosed with PSC 3 and 10 years before the IPAA operation. Two patients had stage II and one patient stage I PSC in their peroperative liver core needle specimens, and three cases, operated on before 1993, had no peroperative liver needle specimen. Four patients (6%) died of cholangiocarcinoma 2, 3, 10, and 19 years, respectively, after restorative proctocolectomy. Of these four, two had had transient elevation of serum alkaline phosphatase, but no other signs of liver disease until the diagnosis of cholangiocarcinoma and thus were not in regular follow-up for PSC. One patient was in regular follow-up for PSC and had PSC-related

cirrhosis but no focal changes in MRI 2 years before cholangiocarcinoma diagnosis. One patient did not participate in follow-up for UC. Five years ago, he became icteric, and PSC and carcinoma of the main bile duct and three carcinomas of the colon were then diagnosed concurrently. He underwent pancreaticoduodenectomy and colectomy. Later, this patient underwent lung resection for pulmonary metastases. In addition, one patient who had been in regular follow-up for cirrhosis stage PSC had carcinoma of the gallbladder occur during follow-up and was operated on.

Overall, three patients were not known to have PSC and were not in regular follow-up, and three patients were in regular follow-up, but their carcinomas were diagnosed because of icterus and not on the basis of follow-up examinations.

Ursodeoxycholic acid therapy

Of 30 patients participating in follow-up examinations, nine used ursodeoxycholic acid therapy. Its use positively correlated with the findings of PSC in MRI (correlation coefficient 0.439; $p<0.05$) and with progression of PSC (correlation coefficient 0.561; $p<0.01$).

Discussion

These results indicate that progression of PSC in patients with UC after restorative proctocolectomy is relatively rare, occurring in only about 13%. In our first follow-up study of 13 patients in which the diagnosis of PSC was based on liver function tests and clinical symptoms, four (31%) showed progression within a mean of 9 years [11]. In that study, PSC prevalence was only 6.1% compared to the prevalence of 11.8% noted in our further study, in which the diagnosis of PSC was based on histological examination of peroperative hepatic core needle specimen [5]. Thus, the patients included in the first study were likely to have had more severe disease than studied later, because 77% of patients in the latter group were non-symptomatic at the time of diagnosis and were detected only in histological examination. Ideally, all UC patients should have imaging of bile ducts due to the problematic diagnosis of PSC, not only laboratory tests and liver biopsy as we did.

Our results suggest that patients in an early stage of PSC at proctocolectomy are at minor risk for progression of liver disease after surgery. If such positive influence of IPAA on PSC exists, it is unclear, if it is due to bowel removal itself or due to secondary effects such as administration of drugs. Likewise, it is not clear, if PSC of symptomless patients had progressed without bowel surgery. Among our patients, all five patients needing liver transplantation after IPAA surgery because of pre-cirrhosis or cirrhosis already had, at proctocolectomy, stage III or IV PSC.

As already stated [8], for patients with PSC, prediction and diagnosis of cholangiocarcinoma and especially of premalignant biliary epithelium are extremely challenging. They have about a 20% lifetime risk for developing cholangiocarcinoma [15, 16]. Six, 9%, of our patients have developed cholangiocarcinoma by now; four (6%) have died of it, and one has metastatic disease. The patient diagnosed with carcinoma of the gall bladder during this follow-up study and with a radical operation, was non-symptomatic at the time of diagnosis. The theory has been to transplant the patients with PSC before they develop cholangiocarcinoma, because results of transplantation after cholangiocarcinoma have been poor. In fact, cholangiocarcinoma has been considered a contraindication for transplantation [17]. Liver transplantation in patients with UC-related PSC after proctocolectomy appeared to be safe and others show it to be safe [18]. The 5-year survival after liver transplantation for PSC in general is 70% [19], for non-malignant PSC, 82% [17], and the 10-year survival for both about 70% [17, 19]. This 10-year mortality of 30% compared to a lifetime risk of 20% for developing cholangiocarcinoma indicates that with the present diagnostic methods, the prevention of cholangiocarcinoma and improvement of survival of this patient group seems impossible. The need for further studies on diagnostic methods to improve the recognition of premalignant changes of the biliary tract and the timing of prophylactic liver transplantation is urgent.

In our follow-up study, MRI detected ductal changes diagnostic for PSC in 72% of the patients and histopathological examination detected PSC-specific changes in 50%. This is line with reports considering the sensitivity of liver biopsy in diagnosing PSC to be poor [20]; MRCP, or ERCP in selected cases, is the diagnostic method of choice [21]. This puts in a different light our earlier figure of 12% for PSC-related changes in peroperative liver needle biopsy [5], indicating that the true prevalence of PSC in these patients is likely to be higher. Even though ERC, MRCP, and PTC are the best imaging modalities in identifying malignant changes in the bile ducts [22], their diagnostic sensitivity is far from optimal. In our patients, liver function tests failed to correlate with stage of PSC, probably mainly because the majority of our patients had relatively mild changes, and the sensitivity of liver function tests alone in diagnosing PSC is poor. Our positive correlation of ursodeoxycholic acid use with stage and progression of PSC indicates that ursodeoxycholic acid is probably chosen for patients with advanced disease and that in these patients does not prevent progression of disease. However, this positive correlation hardly implies that ursodeoxycholic acid worsens PSC due to selection bias.

In conclusion, progression of PSC in patients with minor ductal changes at the time of restorative proctocolectomy is unlikely at least within a decade. Those patients with more advanced disease at surgery are at risk for disease progression and liver transplantation, but after proctocolectomy the transplantation seems to be safe. Unfortunately, we lack proper diagnostic methods to detect premalignant changes of the biliary epithelium, and further efforts are necessary to develop such methods to improve survival. Regular follow-up of patients with minor ductal changes is unnecessary, but patients with more advanced disease may benefit from surveillance with MRI every 2 to 3 years.

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